(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) Publication number: **0 166 596 B1**

(12) **EUROPEAN PATENT SPECIFICATION**

(45) Date of publication of patent specification: **13.03.91**

(51) Int. Cl.5: **C08G 63/66**, A61K 47/00, A61K 9/22

(21) Application number: 85304489.9

(22) Date of filing: 24.06.85

(54) **Biodegradable amphipathic copolymers.**

(30) Priority: 26.06.84 GB 8416234

(43) Date of publication of application:
02.01.86 Bulletin 86/01

(45) Publication of the grant of the patent:
13.03.91 Bulletin 91/11

(84) Designated Contracting States:
AT BE CH DE FR GB IT LI LU NL SE

(56) References cited:
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(73) Proprietor: **IMPERIAL CHEMICAL INDUSTRIES PLC**
**Imperial Chemical House, Millbank**
**London SW1P 3JF(GB)**

(72) Inventor: **Churchill, Jeffrey Richard**
**12 Chiltern Close Sandiway**
**Northwich Cheshire(GB)**
Inventor: **Hutchinson, Francis Gowland**
**29 Woodland Drive**
**Lymm Cheshire, WA13 0BL(GB)**

(74) Representative: **Atkinson, John David et al**
**Imperial Chemical Industries PLC Legal Department: Patents PO Box 6 Bessemer Road**
**Welwyn Garden City Hertfordshire, AL7 1HD(GB)**

**EP 0 166 596 B1**

## Description

This invention relates to biodegradable amphipathic copolymers, and in particular it relates to such copolymers which are rapidly self-dispersible in water to form stable dispersions.

Such copolymers are useful in the manufacture of continuous release formulations of drugs, and are particularly useful for the manufacture of such formulations in which the drug is sensitive to denaturation or degradation by exposure to organic solvents, non-neutral pH or elevated temperature, for example many polypeptides drugs. The copolymers of the present invention permit the manufacture of continuous release formulations of these drugs under conditions which avoid non-neutral pH and elevated temperature, and under conditions such that exposure to organic solvents is avoided, or reduced to minimal levels in solvent mixtures containing only a small proportion of organic solvent.

It is to be understood that in this specification the term "self-dispersible" as applied to a copolymer means a copolymer which, when added to water disperses to form a stable dispersion, without the addition of any surfactant or other additive. In this context, a "stable" dispersion is one which does not significantly agglomerate or precipitate within the time normally required to process the copolymer into a continuous release drug formulation, say 24 hours.

Boswell and Scribner, in United States Patent Number 3,773,919, and Yolles, in United States Patent Number 3,887,699, have described the use of biodegradable polymers, in particular polylactide and poly-(lactide co-glycolide), in the manufacture of sustained release pharmaceutical formulations, and although their disclosures include some polypeptide drugs, we have found that the conditions of manufacture, involving a temperature of at least 130°C., are sufficient to almost completely decompose many polypeptide drugs, so that satisfactory continuous release formulations are not obtainable using the technology of these United States patents.

Furthermore, Hutchinson in European Patent Specification Number 58481 disclosed that, even if processed differently, so as to avoid decomposition of the polypeptide drug, the copolymers described by Boswell and Scribner, and by Yolles, could not be used to obtain satisfactory continuous release formulations of polypeptides. Rather, the release profile was biphasic and discontinuous, an initial release period resulting from surface leaching of the polypeptide being followed by a prolonged "dead phase", in which none or very little, was released, followed in turn by the major release of the polypeptide consequent upon the copolymer matrix absorbing water and being biodegraded.

Hutchinson did, however, disclose that satisfactory continuous release formulations of some polypeptides could be made by using polylactide or poly (lactide co-glycolide) of generally lower molecular weights than those disclosed by Boswell and Scribner, and Yolles, and at lower temperature, but the processing still required the use of organic solvents, to which many polypeptides are labile.

Churchill and Hutchinson in European Patent Specification Number 92918 have disclosed the use of biodegradable amphipathic copolymers, of the general types used in the present invention, in the manufacture of continuous release formulations. However, the copolymers there described are not self-dispersible in water to form stable dispersions, but require the use of organic solvents, which, as indicated above, can be denaturing to polypeptides, in the subsequent processing into a continuous release formulations.

It is an object of the present invention to provide a biodegradable amphipathic copolymer which is self-dispersible in water, and which can therefore be used to manufacture continuous release formulations of drugs without recourse to the use of high temperatures or non-neutral pH, and, for water-soluble drugs such as polypeptides, without exposure of the drug to the use of organic solvents during manufacture. Such copolymers may be self-dispersible as initially synthesised, or copolymers which are not inherently self-dispersible may be rendered so by the processes described herein.

The biodegradable amphipathic copolymers of this invention are also useful for the manufacture of sustained continuous release injectable formulations of drugs which, in contrast with polypeptides, are of low molecular weight and low water solubility. For such drugs, the copolymers of this invention act as very efficient dispersing agents, and can give colloidal suspensions which can be administered by injection to give sustained continuous delivery of lipophilic drugs.

In addition, the biodegradable amphipathic copolymers of this invention can be used to manufacture drug formulations which are targetable to particular organs in the human or animal body. It is known that particles or microspheres of different sizes accumulate in different organs of the body after intravenous injection, depending upon the size of the particles injected. ( For a review, see Tomlinson, "Microsphere Delivery Systems For Drug Targeting And Controlled Release" in Int. J. Pharm. Tech. and Prod. Mfr., 4 , (3), p49-57, 1983). For example, particles of less than 50 nm can pass through the fenestrations of the liver endothelium and become localised, perhaps after lymphatic transport, in the spleen, bone marrow and

possibly tumour tissue. Intravenous, intra-arterial or intraperitoneal injection of particles of approximately 0.1 to 2.0 µm. leads to a rapid clearance of particles from the blood stream by macrophages of the reticuloendothelial system, with eventual localisation of these in the lysosmes of the Kuppfer cells of the liver. Intravenous delivery of particles above 7-12 µm. leads to mechanical filtration by the lungs, while particles between 2 and 12 µm. will become entrapped within the capillary networks of not only the lung but also the liver and spleen. Intra-arterial delivery of particles greater than 12 µm. leads to their blockage of the first capillary bed encountered. The copolymers of this invention can be used to manufacture dispersions of controlled particle size, which can be organ-targeted in the manner described above.

Scheme 1 illustrates diagrammatically the processes involved in this invention.

Thus, according to the invention, there is provided a pharmaceutically or veterinarily acceptable amphipathic, non-cross-linked linear, branched or graft block copolymer, which has a minimum weight average molecular weight of 1000, in which the hydrophobic component is biodegradable or hydrolytically unstable under normal physiological conditions, and the hydrophilic component may or may not be biodegradable or hydrolytically unstable under such conditions, characterised in that it is self-dispersible in water to form a stable dispersion.

According to a further feature of the invention, there is provided a process for the manufacture of a self-dispersible copolymer as defined above, which comprises freeze-drying a frozen stable aqueous dispersion of a pharmaceutically or veterinarily acceptable amphipathic, non-cross-linked linear, branched or graft block copolymer, which has a minimum weight average molecular weight of 1000, in which the hydrophobic component is biodegradable or hydrolytically unstable under such conditions, and the hydrophilic component may or may not be biodegradable or hydrolytically unstable under such conditions.

When an "aqueous dispersion" is referred to herein, it is to be understood as comprising a dispersion in water alone, or in water containing a small proportion, for example up to 10%, of a water-miscible organic solvent.

The copolymers which may be used as the starting materials in the above process are those described in European Patent Specification No. 92918, referred to above.

The frozen, stable aqueous dispersion used as the starting material for the above process may be obtained by dissolving the copolymer described immediately above, in its non-self-dispersible form, as initially synthesised, in a minimum amount of a water-miscible solvent, which either has a low boiling point, say below 100° C., for example methanol or ethanol, or is freeze- driable, for example dioxan or acetic acid, vigorously agitating said solution while an excess of water is added slowly, to form an extremely fine, stable aqueous dispersion, and then freezing said dispersion.

According to a further feature of the invention, there is provided a solid, copolymer/drug powder material comprising up to 99% by weight of a drug, the remainder being a pharmaceutically or veterinarily acceptable amphipathic, non-cross-linked linear, branched or graft block copolymer as defined above, characterised in that said solid, powder material is self-dispersible in water to form a stable dispersion.

According to a further feature of the invention, there is provided a process for the manufacture of a solid, copolymer/drug powder material, as defined immediately above, which comprises freeze-drying a frozen, stable aqueous dispersion of the copolymer and the drug.

The frozen, stable aqueous dispersion used as the starting material for the above process may be obtained, when the drug is water-soluble, for example a polypeptide, by dispersing a self-dispersible copolymer, as defined above, in water, buffering the dispersion to physiological or neutral pH, mixing the buffered dispersion with an aqueous solution of the water-soluble drug, and freezing the resulting copolymer/ drug dispersion.

Particular water-soluble polypeptides which may be used in this invention are, for example, oxytocin, vasopressin, adrenocorticotrophic hormone (ACTH), epidermal growth factor (EGF), transforming growth factor antagonists, prolactin, luliberin or luteinizing hormone releasing hormone (LH-RH), LH-RH agonists or antagonists, growth hormone, growth hormone releasing factor, insulin, somatostatin, bombesin antagonists, glucagon, interferon, gastrin, tetragastrin, pentagastrin, urogastrone, secretin, calcitonin, enkephalins, endorphins, angiotensins, renin, bradykinin, bacitracins, polymyxins, colistins, tyrocidin, gramicidines, and synthetic analogues and modifications and pharmaceutically-active fragments thereof, monoclonal antibodies and soluble vaccines.

When the drug is water-insoluble, the frozen, stable aqueous dispersion used in the above process may be obtained by dissolving the drug and the self-dispersible copolymer in a minimum amount of a water-miscible organic solvent, for example dioxan, acetic acid, acetonitrile, methanol or ethanol, slowly adding an excess of water to the vigorously agitated solution to produce a fine, stable dispersion, and then freezing the dispersion.

Any drug of low water-solubility is appropriate for use in this aspect of the invention.

Alternatively, one of the freeze-drying processes may be avoided by taking the copolymer in its non-self-dispersible form, dissolving it in a water-miscible organic solvent, precipitating it as a fine dispersion by slow addition of an excess of water with vigorous agitation, adding a solution of a drug, either in water, if the drug is water-soluble, or in a water miscible organic solvent or in a mixture thereof with water if the drug is water-insoluble, to the copolymer dispersion, and then freezing and freeze-drying the total mixture.

Certain pharmaceutically or veterinarily acceptable amphipathic, non-cross-linked linear, branched or graft block copolymers, which have a minimum weight average molecular weight of 1000, in which the hydrophobic component is biodegradable or hydrolytically unstable under normal physiological conditions, and in which the hydrophilic component may or may not be biodegradable or hydrolytically unstable under such conditions, are self-dispersible in water as synthesised. These are copolymers which contain a large proportion, that is, more than 50%, of hydrophile relative to hydrophobe, or copolymers in which the hydrophobe is of low molecular weight, for example $M_w$ of less than 5000.

Additionally, the structure of the copolymer, and the nature of the individual hydrophilic and hydrophobic polymers therein, control the degree of self-dispersibility in water of the copolymer obtained therefrom. Thus, for example, polylactide-graft-polyvinylpyrrolidone (PVP) is self-dispersing when it contains 50% or more of PVP, even though the polylactide may be of relatively high molecular weight, for example $M_w$ of greater than 30,000; and polylactide/polyethylene glycol 1900 (equal weights) is self-dispersible. However, polylactide/polyethylene glycol 5000 (equal weights) is self-dispersible with difficulty, and above this molecular weight the copolymers are not immediately self-dispersible in water, but require initially the addition of a small proportion of an organic solvent, which can subsequently be removed by evaporation or freeze-drying.

As indicated above, the materials of this invention are useful in the manufacture of sustained continuous release formulations of drugs. As has been described above, a mixture of a copolymer of the invention with a drug can be manufactured under such conditions that the drug is not exposed to high temperature, to non-neutral pH, to high concentrations of organic solvent, or to organic solvent at elevated temperature, and such copolymer-drug mixtures can be processed into suitable pharmaceutical or veterinary formulations by conventional procedures, for example by compression moulding at low temperatures (many can be conveniently compression moulded at about 60°C., well below the decomposition temperature of most drugs, including polypeptide drugs which are among those which are most susceptible to decomposition at elevated temperatures), to form implantable depot formulations as described, for example, by Hutchinson (European Patent Specification Number 58481) and by Churchill and Hutchinson (European Patent Specification Number 92918), which give a sustained continuous release of the drug. Alternatively, for water-insoluble drugs, the copolymer-drug mixture can be simply dispersed into sterile water to give a fine aqueous dispersion which can be used as an injectable, sustained continuous release formulation, or, if the particle size is suitably controlled, a formulation which is targeted to a particular organ, as described above.

The particle size of such an aqueous dispersion can be controlled within fairly close limits by controlling the particle size of the copolymer used. This is achieved during the manufacture of the self-dispersible form of the copolymer used, and is achieved by suitable adjustment of the rate of addition of water to the solution of copolymer in the freeze-driable, water-miscible solvent, and control of the rate of agitation during this process. The particle size of the dispersion so obtained may be measured in conventional manner, for example by optical microscopy, Coulter counter or nanosizer.

Useful co-excipients in the manufacture of sustained, continuous release formulations of polypeptides using the above-described copolymer/drug mixtures, are low or high molecular weight, water soluble polymers which are compatible, or partially compatible therewith, such as gelatin, polyvinyl-pyrrolidone, dextran, polyethylene glycols, sodium alginate and water soluble, synthetic, non-therapeutic polypeptides. Such co-excipients provide additional hydrophilic regions, or pores, in the polymer matrix, and also stabilise the tertiary structure of the polypeptide by chain entanglement, which is achievable by virtue of their being compatible or partially compatible with the polypeptide.

Example 1

Two grammes of an AB type biodegradable copolymer comprising 25% by weight of a methoxypolyethylene glycol of molecular weight 5900 (component A) and 75% by weight of poly(D,L-lactide) (component B) were dissolved in glacial acetic acid (2 mL), and the solution was stirred vigorously while distilled water (21 ml.) was added slowly, to produce an extremely fine dispersion. The dispersion was frozen, and freeze dried at 0.01 mm. of mercury (13.3 Pa) for 24 hours, to give a dry powder copolymer.

On addition of the dry powder to water, with stirring, it redispersed to form a very fine dispersion.

Example 2

The dry powder copolymer of Example 1 (0.5 g.) was dispersed with vigorous stirring into distilled water (5 ml.) containing sodium azide (0.01%), and the dispersion was buffered to pH8 with 0.1N sodium hydroxide. Bovine serum albumin (BSA) (0.125 g.) was dissolved in distilled water (1.0 ml.) and $^{14}$C-methylated BSA (10 ul. of a 5 uCi per ml. solution in 0.01M sodium phosphate buffer) was added, the BSA solution was added to the copolymer dispersion, and the mixture was frozen, then freeze dried at 0.01 mm. of mercury (13.3 Pa) for 24 hours.

The freeze dried product was moulded at 60-70° to give slabs 1 cm. square and of thickness 0.2 cm., 0.09 cm. and 0.04 cm. The different slabs were each separately immersed in 2 ml. of phosphate buffered saline (pH 7.4) containing 0.02% sodium aside, at 37° C. At intervals, the medium was removed and replaced with fresh buffer, and the radioactivity released into the removed medium was assayed.

| Time | Cumulative % BSA released | | |
|---|---|---|---|
| | 0.2 cm. slab. | 0.09 cm. slab | 0.04 cm. slab |
| 1 hour | 10.8 | 23.8 | 46.6 |
| 4 hours | 23.4 | 48.5 | 77.3 |
| 24 hours | 64.4 | 86.5 | 86.7 |
| 3 days | 86.4 | 92.2 | 88.8 |
| 12 days | 90.1 | 92.3 | 90.9 |

Example 3

2.5 Grammes of a poly (D,L-lactide-coglycolide)-graft(polyvinylpyrrolidone) copolymer, containing 50% by weight of poly (D,L-lactide-coglycolide) comprising equimolar proportions of lactide and glycolide, and 50% by weight of polyvinyl-pyrrolidone, were dissolved in glacial acetic acid (5 ml.) and stirred vigorously while distilled water (20 ml.) was added slowly, to produce a very fine dispersion, which was then frozen and freeze dried at 0.1 mm. of mercury (13.3 Pa) for 24 hours, to give a dry powder copolymer.

On addition of the dry powder copolymer to water, with stirring, it redispersed almost immediately to form a very fine dispersion.

Example 4

2.0 Grammes of an ABA type biodegradable block copolymer comprising 80% by weight of poly(D,L-lactide) (component A) and 20% by weight of polyethylene gylcol of molecular weight 2000 (component B) was added to absolute ethanol (3 ml.) and stirred vigorously while water (1.5 ml.) was added slowly to produce an extremely fine dispersion. A further 15 ml. of water was added, with vigorous agitation, to give a dilute dispersion of the copolymer, which was then buffered to pH8 by addition of 0.1N sodium hydroxide.

Bovine serum albumin (BSA) (0.5 g.) was dissolved in water (5 ml.) and $^{14}$C-methylated BSA (70 ul. of

a 5uCi/ml. solution in 0.01M sodium phosphate) was added. The BSA solution was then mixed with the copolymer dispersion, frozen, and freeze dried at 0.01 mm. of mercury (13.3 Pa) for 30 hours.

The freeze-dried powder was moulded at 60°C. to give slabs 1 cm. square and of thickness 0.36 cm., 0.16 cm. and 0.06 cm. The different slabs were each separately immersed in 2 ml. of phosphate buffered saline, pH 7.4, at 37°C. At intervals, the medium was removed and replaced with fresh buffer, and the radioactivity released into the removed medium was assayed.

| Time | Cumulative % BSA released | | |
|---|---|---|---|
| | 0.36 cm. slab. | 0.16 cm. slab | 0.06 cm. slab |
| 1 hour | 8.5 | 12.8 | 23.8 |
| 4 hours | 17.0 | 28.0 | 58.4 |
| 24 hours | 40.3 | 58.2 | 87.2 |
| 4 days | 65.8 | 82.0 | 96.0 |
| 11 days | 82.1 | 96.0 | 100 |

Example 5

Purified methoxypolyethylene glycol of molecular weight 1900, rigorously dried at 160°C. for 1 hour at 0.1 mm. of mercury (13.3 Pa) (10 g.) and freshly prepared, rigorously dried D,L-lactide (10 g.) were stirred under nitrogen at 160°C., stannous octoate (stannous 2-ethylhexanoate) (50 ul.) was added, and the mixture was kept at 160°C. for 3 hours, to give a straw-coloured, slightly viscous liquid which solidified on cooling. The solid product (0.5 g.) was added to distilled water (5 ml.) and stirred at 37°C. for 18 hours, after which time it has formed an extremely fine dispersion or colloidal suspension, which appeared entirely clear, except for a very faint blue haze when held to the light. In contrast, a simple mixture of the same methoxypolyethyleneglycol (0.25 g.) and poly(D,L-lactic acid) (0.25 g.) in distilled water (5 ml.) did not give a dispersion after stirring at 37°C for a similar period, but the polyester remained as a semi-solid, non-dispersed phase.

Example 6

An AB block copolymer of poly(d,l-lactide) and methoxy-polyethylene glycol containing 50% (wt) polyester and 50% (wt) of polyether was prepared by the ring opening polymerisation of d,l-lactide in the presence of methoxypolyethylene glycol 5000 at 160°C. using an organotin catalyst.

100mg. of the block copolymer and 10mg. of an antioestrogen, ICI 189150, which has very low aqueous solubility, were dissolved in 0.4ml. of glacial acetic acid, and 2ml. of water were added slowly with vigorous agitation to give a colloidal suspension of drug/polymer in the acetic acid/water mixture. The mixture was frozen and freeze dried at 0.01mm.Hg. (13.3 Pa) for 24hr., to give a solid freeze dried product.

On addition of 0.9% sodium chloride solution in water the freeze dried product redispersed to give a stable dispersion suitable for injection.

Claims

1. A pharmaceutically or veterinarily acceptable amphipathic, non-cross-linked linear, branched or graft block copolymer, which has a minimum weight average molecular weight of 1000, in which the hydrophobic component is biodegradable or hydrolytically unstable under normal physiological conditions, and the hydrophilic component may or may not be biodegradable or hydrolytically unstable under such conditions, characterised in that it is self-dispersible in water to form a stable dispersion.

2. A copolymer as claimed in claim 1 which either has a large proportion of hydrophile to hydrophobe or has a hydrophobe weight average molecular weight of less than 5000.

3. A process for the manufacture of a self-dispersible copolymer as defined in claim 1, which comprises freeze-drying a frozen stable aqueous dispersion of a pharmaceutically or veterinarily acceptable amphipathic, non-cross-linked linear, branched or graft block copolymer, which has a minimum weight average molecular weight of 1000, in which the hydrophobic component is biodegradable or hydrolytically unstable under such conditions, and the hydrophilic component may or may not be biodegradable or hydrolytically unstable under such conditions.

4. A process for the manufacture of a frozen aqueous dispersion of a pharmaceutically or veterinarily acceptable amphipathic, non-cross-linked linear, branched or graft block copolymer, which has a minimum weight average moleculare weight of 1000, in which the hydrophobic component is biodegradable or hydrolytically unstable and the hydrophilic component may or may not be biodegradable or hydrolytically unstable, which comprises dissolving such a copolymer in the non-self-dispersible form in a water-miscible solvent which either has a low boiling point or is freeze-driable, vigorously agitating said solution while an excess of water is added, and freezing the resulting dispersion.

5. A solid, copolymer/drug powder material comprising up to 99% by weight of a drug, the remainder being a pharmaceutically or veterinarily acceptable amphipathic, non-cross-linked linear, branched or graft block copolymer as claimed in claim 1 characterised in that said solid, powder material is self-dispersible in water to form a stable dispersion.

6. A copolymer/drug powder material as claimed in claim 5 wherein the drug is water-soluble and is selected from oxytocin, vasopressin, adrenocorticotrophic hormone (ACTH), epidermal growth factor (EGF), transforming growth factor antagonists, prolactin, luliberin or lutsinizing hormone releasing hormone (LH-RH), LH-RH agonists or antagonists, growth hormone, growth hormone releasing factor, insulin, somatostatin, bombesin antagonists, glucagon, interferon, gastrin, tetragastrin, pentagastrin, urogastrone, secretin, calcitonin, enkephalins, endorphins, angiotensins, renin, bradyklnin, bacitracins, polymyxins, colistins, tyrocidin, gramicidines and synthetic analogues and modifications and pharmaceutically-active fragments thereof, monoclonal antibodies and soluble vaccines.

7. A process for the manufacture of a solid, copolymer/drug powder material as claimed in claim 5, characterised by freeze-drying a frozen, stable aqueous dispersion of the copolymer and the drug.

8. A process for the manufacture of a frozen, stable aqueous dispersion of a copolymer and a water-soluble drug, as defined in claim 7, characterised by dispersing a self-dispersible copolymer, as claimed in claim 1, in water, buffering the dispersion to physiological or neutral pH, mixing the buffered dispersion with an aqueous solution of the water-soluble drug, and freezing the resulting copolymer/drug dispersion.

9. A process for the manufacture of a frozen, stable aqueous dispersion of a copolymer and a water-insoluble drug, as defined in claim 7, characterised by dissolving the drug and the self-dispersible copolymer in a minimum amount of a water-miscible organic solvent, slowly adding an excess of water to the vigorously agitated solution of produce a fine, stable dispersion, and then freezing the dispersion.

10. A process for the manufacture of a frozen, stable aqueous dispersion of a copolymer and a drug, as defined in claim 7, characterised by dissolving the copolymer, in its non-self-dispersible form, in a water-miscible, organic solvent, slowly adding an excess of water to the vigorously agitated solution, adding a solution of the drug, either in water if the drug is water-soluble, or in a water-miscible solvent

or in a mixture thereof with water if the drug is water-insoluble, to the copolymer dispersion, and then freezing the copolymer/drug dispersion so obtained.

## Revendications

1. Copolymère séquencé linéaire, ramifié ou greffé amphipathique, non réticulé, acceptable pour un usage pharmaceutique ou vétérinaire, qui possède une moyenne pondérale minimale du poids moléculaire égale à 1000, dans lequel la partie hydrophobe est biodégradable ou hydrolytiquement instable dans des conditions physiologiques normales, et la partie hydrophile peut être ou non biodégradable ou hydrolytiquement instable dans de telles conditions, caractérisé en ce qu'il est auto-dispersable dans l'eau pour former une dispersion stable.

2. Copolymère suivant la revendication 1, qui présente un rapport élevé de la partie hydrophile à la partie hydrophobe ou bien qui possède une moyenne en poids du poids moléculaire de la partie hydrophobe inférieure à 5000.

3. Procédé de production d'un copolymère autodispersable suivant la revendication 1, qui consiste à lyophiliser une dispersion aqueuse stable congelée d'un copolymère séquencé linéaire, ramifié ou greffé amphipathique, non réticulé, acceptable pour un usage pharmaceutique ou vétérinaire, qui possède une moyenne pondérale minimale du poids moléculaire égale à 1000, dans lequel la partie hydrophobe est biodégradable ou hydrolytiquement instable dans de telles conditions, et la partie hydrophile peut être ou non biodégradable ou hydrolytiquement instable dans de telles conditions.

4. Procédé de production d'une dispersion aqueuse congelée d'un copolymère séquencé linéaire, ramifié ou greffé amphipathique, non réticulé, acceptable pour un usage pharmaceutique ou vétérinaire, qui possède une moyenne pondérale minimale du poids moléculaire égale à 1000, dans lequel la partie hydrophobe est biodégradable ou hydrolytiquement instable et la partie hydrophile peut être ou non biodégradable ou hydrolytiquement instable, qui consiste à dissoudre un tel copolymère sous forme non auto-dispersable dans un solvant miscible à l'eau qui possède un bas point d'ébullition ou bien peut être lyophilisé, à agiter énergiquement ladite solution tout en ajoutant un excès d'eau et à congeler la dispersion résultante.

5. Matière solide en poudre constituée d'un copolymère et d'un médicament, comprenant jusqu'à 99% en poids d'un médicament, le reste étant un copolymère séquencé linéaire, ramifié ou greffé amphipathique, non réticulé, acceptable pour un usage pharmaceutique ou vétérinaire, suivant la revendication 1, caractérisée en ce que ladite matière solide en poudre est auto-dispersable dans l'eau pour former une dispersion stable.

6. Matière en poudre constituée d'un copolymère et d'un médicament suivant la revendication 5, dans laquelle le médicament est hydrosoluble et est choisi entre l'ocytocine, la vasopressine, l'hormone adrénocorticotrope (ACTH), le facteur de croissance épidermique (EGF), des antagonistes du facteur de croissance de transformation, la prolactine, la lulibérine ou l'hormone de libération de la lutéinostimuline (LH-RH), des agonistes ou des antagonistes de la LH-RN, l'hormone de croissance, le facteur de libération de l'hormone de croissance, l'insuline, la somatostatine, des antagonistes de la bombésine, le glucagon, l'interféron, la gastrine, la tétragastrine, la pentagastrine, l'urogastrone, la sécrétine, la calcitonine, les enképhalines, les endorphines, les angiotensines, la rénine, la bradykinine, les bacitracines, les polymyxines, les colistines, la tyrocidine, les gramicidines et des analogues et variantes synthétiques ainsi que leurs fragments pharmaceutiquement actifs, des anticorps monoclonaux et des vaccins solubles.

7. Procédé de production d'une matière solide en poudre constituée d'un copolymère et d'un médicament suivant la revendication 5, caractérisé en ce qu'il consiste à lyophiliser une dispersion aqueuse stable congelée du copolymère et du médicament.

8. Procédé de production d'une dispersion aqueuse stable congelée d'un copolymère et d'un médicament hydrosoluble suivant la revendication 7, caractérisé en ce qu'il consiste à disperser un copolymère auto-dispersable, suivant la revendication 1, dans de l'eau, à tamponner la dispersion au pH physiologi-

que ou à pH neutre, à mélanger la dispersion tamponnée à une solution aqueuse du médicament hydrosoluble et à congeler la dispersion résultante de copolymère et de médicament.

9. Procédé de production d'une dispersion aqueuse stable congelée d'un copolymère et d'un médicament insoluble dans l'eau suivant la revendication 7, caractérisé en ce qu'il consiste à dissoudre le médicament et le copolymère auto-dispersable dans une quantité minimale d'un solvant organique miscible à l'eau, à ajouter lentement un excès d'eau à la solution sous agitation énergique pour produire une dispersion fine stable, puis à congeler la dispersion.

10. Procédé de production d'une dispersion aqueuse stable congelée d'un copolymère et d'un médicament suivant la revendication 7, caractérisé en ce qu'il consiste à dissoudre le copolymère, sous sa forme non autodispersable, dans un solvant organique miscible à l'eau, à ajouter lentement un excès d'eau à la solution sous agitation énergique, à ajouter une solution du médicament, dans de l'eau si le médicament est hydrosoluble ou bien dans un solvant miscible à l'eau ou dans un mélange de ce solvant avec de l'eau si le médicament est insoluble dans l'eau, à la dispersion de copolymère, puis à congeler la dispersion de copolymère et de médicament ainsi obtenue.

**Ansprüche**

1. Pharmazeutisch oder veterinär zulässiges, amphipathisches, nichtvernetztes, lineares, verzweigtes oder gepfropftes Blockcopolymer mit einem Mindestdurchschnittsmolekulargewicht nach dem Gewichtsmittel von 1000, in welchem die hydrophobe Komponente unter normalen physiologischen Bedingungen biologisch abbaubar oder hydrolytisch instabil ist und in welchem die hydrophile Komponente unter solchen Bedingungen biologisch abbaubar oder hydrolytisch instabil sein kann oder auch nicht, dadurch gekennzeichnet, daß es in Wasser unter Bildung einer stabilen Dispersion selbstdispergierbar ist.

2. Copolymer nach Anspruch 1, welches entweder ein großes Verhältnis von hydrophiler Komponente zu hydrophober Komponente oder ein Durchschnittsmolekulargewicht nach dem Gewichtsmittel der hydrophoben Komponente von weniger als 5000 aufweist.

3. Verfahren zur Herstellung eines selbstdispergierbaren Copolymers gemäß Anspruch 1, bei welchem eine gefrorene, stabile wäßrige Dispersion eines pharmazeutisch oder veterinär zulässigen, amphipathischen, nichtvernetzten, linearen, verzweigten oder gepfropften Blockcopolymers mit einem Mindestdurchschnittsmolekulargewicht nach dem Gewichtsmittel von 1000 gefriergetrocknet wird, in welchem die hydrophobe Komponente unter solchen Bedingungen biologisch abbaubar oder hydrolytisch instabil ist und in welchem die hydrophile Komponente unter solchen Bedingungen biologisch abbaubar oder hydrolytisch instabil sein kann oder auch nicht.

4. Verfahren zur Herstellung einer gefrorenen wäßrigen Dispersion eines pharmazeutisch oder veterinär zulässigen, amphipathischen, nichtvernetzten, linearen, verzweigten oder gepfropften Blockcopolymers mit einem Mindestdurchschnittsmolekulargewicht nach dem Gewichtsmittel von 1000, in welchem die hydrophobe Komponente biologisch abbaubar oder hydrolytisch instabil ist und in welchem die hydrophile Komponente biologisch abbaubar oder hydrolytisch instabil sein kann oder auch nicht, bei welchem Verfahren ein solches Copolymer in der nicht selbstdispergierbaren Form in einem mit Wasser mischbaren Lösungsmittel, welches entweder einen niedrigen Siedepunkt aufweist oder gefriertrockenbar ist, aufgelöst wird, die Lösung heftig gerührt wird, während ein Wasserüberschuß zugegeben wird, und die erhaltene Dispersion gefroren wird.

5. Festes Copolymer/Medikament-Pulvermaterial, welches bis zu 99 Gew.% eines Medikaments enthält, wobei der Rest ein pharmazeutisch oder veterinär zulässiges, amphipathisches, nichtvernetztes, lineares, verzweigtes oder gepfropftes Blockcopolymer nach Anspruch 1 ist, dadurch gekennzeichnet, daß das feste Pulvermaterial in Wasser unter Bildung einer stabilen Dispersion selbstdispergierbar ist.

6. Copolymer/Medikament-Pulvermaterial nach Anspruch 5, bei welchem das Medikament wasserlöslich ist und ausgewählt ist aus Oxytocin, Vasopressin, adrenocorticotrophischem Hormon (ACTH), epidermem Wachstumsfaktor (EGF), Transformationswachstumsfaktorantagonisten, Prolactin, Luliberin oder

Luteinisierungshormon freisetzendem Hormon (LH-RH), LH-RH-Agonisten oder -Antagonisten, Wachstumshormon, Wachstumshormonfreisetzungsfaktor, Insulin, Somatostatin, Bombesinantagonisten, Glucagon, Interferon, Gastrin, Tetragastrin, Pentagastrin, Urogastron, Secretin, Calcitonin, Enkephalinen, Endorphinen, Angiotensinen, Renin, Bradykinin, Bacitracinen, Polymyxinen, Colistinen, Tyrocidin, Gramicidinen und synthetischen Analogen und Modifikationen und pharmazeutisch aktiven Fragmenten davon, monoklonalen Antikörpern und löslichen Vaccinen.

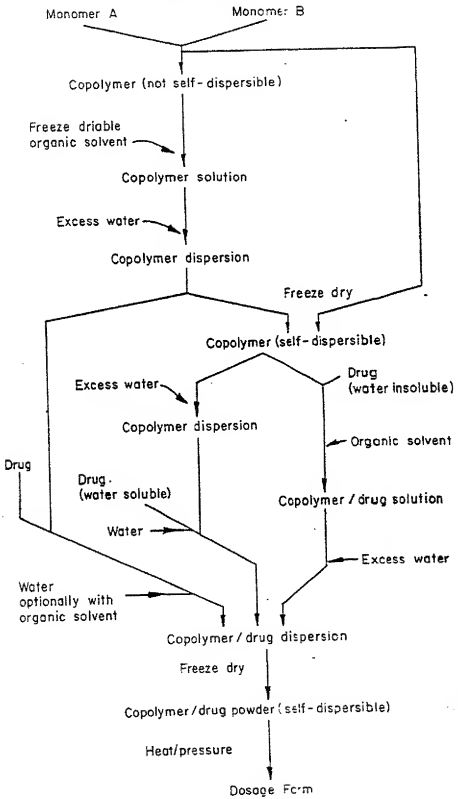
7. Verfahren zur Herstellung eines festen Copolymer/ Medikament-Pulvermaterials nach Anspruch 5, dadurch gekennzeichnet, daß eine gefrorene, stabile wäßrige Dispersion des Copolymers und des Medikaments gefriergetrocknet wird.

8. Verfahren zur Herstellung einer gefrorenen, stabilen wäßrigen Dispersion eines Copolymers und eines wasserlöslichen Medikaments nach Anspruch 7, dadurch gekennzeichnet, daß ein selbstdispergierbares Copolymer nach Anspruch 1 in Wasser dispergiert wird, die Dispersion auf einen physiologischen oder neutralen pH-Wert gepuffert wird, die gepufferte Dispersion mit einer wäßrigen Lösung des wasserlöslichen Medikaments gemischt wird und die erhaltene Copolymer/Medikament-Dispersion gefroren wird.

9. Verfahren zur Herstellung einer gefrorenen, stabilen wäßrigen Dispersion eines Copolymers und eines wasserunlöslichen Medikaments nach Anspruch 7, dadurch gekennzeichnet, daß das Medikament und das selbstdispergierbare Copolymer in einer Mindestmenge eines mit Wasser mischbaren organischen Lösungsmittels aufgelöst wird, langsam ein Wasserüberschuß zu der heftig gerührten Lösung zugegeben wird, um eine feine, stabile Dispersion herzustellen, und hierauf die Dispersion gefroren wird.

10. Verfahren zur Herstellung einer gefrorenen, stabilen wäßrigen Dispersion eines Copolymers und eines Medikaments nach Anspruch 7, dadurch gekennzeichnet, daß das Copolymer in seiner nicht selbstdispergierbaren Form in einem mit Wasser mischbaren organischen Lösungsmittel aufgelöst wird, langsam ein Wasserüberschuß zu der heftig gerührten Lösung zugegeben wird, eine Lösung des Medikaments entweder in Wasser, sofern das Medikament wasserlöslich ist, oder in einem mit Wasser mischbaren Lösungsmittel oder in einem Gemisch desselben mit Wasser, sofern das Medikament in Wasser unlöslich ist, zur Copolymer-Dispersion zugegeben wird und hierauf die so erhaltene Copolymer/Medikament-Dispersion gefroren wird.

## SCHEME I


Monomer A
Monomer B
Copolymer (not self-dispersible)
Freeze driable organic solvent
Copolymer solution
Excess water
Copolymer dispersion
Freeze dry
Copolymer (self-dispersible)
Excess water
Drug (water insoluble)
Copolymer dispersion
Organic solvent
Drug
Drug (water soluble)
Copolymer / drug solution
Water
Excess water
Water optionally with organic solvent
Copolymer / drug dispersion
Freeze dry
Copolymer / drug powder (self-dispersible)
Heat/pressure
Dosage Form